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Review Article

Moxibustion for treating rheumatoid arthritis: A systematic review and meta-analysis of randomized controlled trials

Zhi-ling Sun *,[1], Xiao Xu [1], Shi-zheng Du, Xing Jiang

Nursing College, Nanjing University of Chinese Medicine, Nanjing, China

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Abstract

Introduction: Moxibustion is widely used in China and other East Asian countries to manage the symptom of rheumatoid arthritis (RA) and to lessen the adverse effects of western medicine. The purpose of this systematic review was to evaluate the available evidence from randomized controlled trials (RCTs) of moxibustion for treating patients with rheumatoid arthritis (RA).

Methods: Seven Chinese and English databases were searched to November 2013 from their inception. Eligible RCTs were included if moxibustion was used either alone or in combination with Western medicine for treating rheumatoid arthritis. Study selection, data extraction, and validation was performed independently by two reviewers. Cochrane criteria for risk of bias was used to assess the methodological quality of the trials.

Results: Eight RCTs met the inclusion criteria, and most were of low methodological quality. Meta-analysis showed favorable effects of moxibustion on the response rate, either alone [RR = 1.18, 95%CI (1.03, 1.35), $p = 0.02$; heterogeneity: $Chi^2 = 1.11$, $p = 0.77$, $I^2 = 0\%$] or the combination with Western medicine therapy [RR = 1.28, 95%CI (1.12, 1.47), $p = 0.0004$; heterogeneity: $Chi^2 = 1.96$, $p = 0.58$, $I^2 = 0\%$]. When compared with Western medicine therapy, Western medicine plus moxibustion therapy showed a favorable statistically significant effect on a reduction on American College of Rheumatology (ACR) 50 [RR = 1.57, 95%CI (1.25, 1.99), $p = 0.0001$; heterogeneity: $Chi^2 = 2.87$, $p = 0.58$, $I^2 = 0\%$], whereas it failed to do so on American College of Rheumatology (ACR) 20. Additionally, when compared with western medicine therapy alone, meta-analysis of three RCTs suggested favorable but no statistically significant effects of moxibustion plus western medicine on the control of disease activities of rheumatoid arthritis.

Conclusions: It is difficult to draw firm conclusions on whether moxibustion is an effective intervention for treating RA due to the small sample size of eligible RCTs and the high risk of bias among the available RCTs. Further rigorous RCTs are warranted but need to overcome methodological shortcomings of the existing evidence.

Keywords: Rheumatoid arthritis; Moxibustion; Systematic review; Meta-analysis; Randomized controlled trials

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder of unknown etiology affecting approximately 0.2–1% of the world's population [1–3]. It can be the consequence of a pathological process characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic complications. The most common clinical symptoms include symmetrical arthralgia, mainly present in the hands and feet, stiffness, joint damage, and loss of physical function [2,3]. RA is a global health problem both in developed and developing countries and results in significant negative effects on quality of health life in terms of the persistent pain, fatigue, disability, as well as the heavy economic burden associated with disease progression [4–12].

Currently, the treatment strategy is to initiate aggressive therapy soon after diagnosis [2]. Compared with the conventional drug therapy, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommended that the use of biologic agents can be highly beneficial for control inflammatory activity and devel-

* Corresponding author at: Nursing College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province 210023, China. Tel.: +86 025 85811639; fax: +86 025 85811649.

E-mail address: xux8152@gmail.com (Z.-l. Sun).

[1] These authors contributed equally to this paper.

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opment of erosions in many RA patients [13,14]. Sometimes these treatment strategies fail or produce only partial responses, and the most impressive drugs may be too expensive for clients in developing countries [3]. Hence, RA is still a dilemma in modern medicine.

Moxibustion is an important integral part of traditional Chinese medicine (TCM). It is described as a technique that applies heat which is generated by burning herbal preparations containing *Artemisia vulgaris* to stimulate acupuncture points [15]. It is generally classified into direct and indirect moxibustion. A moxa cone placed on the acupuncture point and ignited is called direct moxibustion. Traditionally it is subdivided into no scarring moxibustion, and scarring moxibustion according to the degree of burning over the skin. In the former, the moxa cone is replaced by a new one when the patient feels a warming sensation. The moxibustion on an acupuncture point requires repetition of this process 3–7 times. In the latter, the moxa cone is burned on the skin until blisters are formed. In indirect moxibustion, some insulating materials (ginger, salts, herbal cake, etc.) are placed between the moxa cone and the skin. Historically, the Spiritual Pivot (Ling Shu, Guan Neng Pian) says: "When needling does not work, moxibustion may be appropriate."

In comparison to acupuncture, moxibustion is less well known in western countries, which is due in part to the lack of the modern medical evidence. Recently, a bibliometric analysis of papers published from 1954 to 2007 in China, showed that 364 kinds of diseases, including rheumatoid arthritis, were being treated with moxibustion [16]. Various systematic reviews have investigated the effects of moxibustion on rheumatic conditions [17], osteoarthritis [18], and pain conditions [19]. Nevertheless, there have been no systematic reviews specifically focusing on the moxibustion treatment of RA. As moxibustion originated in China, it was likely that more studies would be carried out in China and therefore in more Chinese databases were included in the searched compared to previous reviews.

The aim of this study is to update and critically evaluate the efficacy and safety of moxibustion in treating RA. This was achieved by a systematic review and meta-analysis of randomized controlled trials (RCTs) that involve moxibustion.

Materials and methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines using a pre-specified protocol, including the search strategy, inclusion criteria for the articles and methods for the analysis, which was developed prior to the beginning of the study [20].

Data sources

Databases searched included; Medline, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and three Chinese databases [WanFang Med Database, Chinese BioMedical Database, China National Knowledge Infrastructure (CNKI)] from their inception to November 2013. Search strategies are shown in Appendix A, and these search terms were slightly modified for other databases. Finally, review articles were searched, and, lists of selected articles were screened and checked for potential eligible studies.

Selections of studies

Only randomized controlled trials (RCTs) related to the effects of moxibustion on RA were included in this systematic review. Trials published in the form of dissertations and abstracts were also selected as eligible studies. Further, these studies had to meet the following inclusion criteria:

P (population): patients aged over 18 with rheumatoid arthritis in any joint.
I (intervention): Studies that compared moxibustion with western medicine or moxibustion plus western medicine with western medicine alone. Studies in which moxibustion was part of a complex intervention were excluded as were studies where other traditional Chinese therapies (e.g. acupuncture, Chinese herbals, Chinese patent medicine) were used as an adjunct treatment in conjunction with moxibustion.
C (comparison): The western medical interventions were confirmed as reference standard therapies for RA in the control group. Studies were excluded if the control group treatments were not relevant to the western medical therapies, or the other traditional Chinese therapies (e.g. acupuncture, Chinese herbals, Chinese patent medicine) were used as an adjunct treatment in conjunction with the western medical therapies.
O (outcomes): The primary outcome included in this review was the efficacy of response of RA to treatment with moxibustion by the American College of Rheumatology (ACR) outcome measures ACR20, 50 and 70, which includes a count of tender and swollen joints, patient assessment of global pain, physician assessment of disease activity, a health assessment questionnaire (HAQ) and laboratory parameters (erythrocyte sedimentation rate or C-reactive protein) [21]. The ACR measures have been successfully applied in other meta-analyses [22]. In addition, the total response rate which is mostly based on the guiding principles of clinical research on new drugs of traditional Chinese medicine was also a primary outcome in this review. Similar to ACR rate, response rate include a count of tender and swollen joints, morning stiffness duration, mean grip strength, patient assessment of global pain and laboratory parameters (erythrocyte sedimentation rate, C-reactive protein and rheumatoid factor). The secondary outcome included Disease Activity Score-28 (DAS28), which is a useful tool for monitoring RA patients. Stable low values for the DAS28 can indicate uncomplicated course of RA [23].

Finally, studies with designs that compared two different forms of moxibustion or different sessions of moxibustion were excluded. Trials testing warm needle moxibustion on the top of acupuncture needle were also excluded because this type of intervention cannot evaluate the effects of moxibustion alone.

Data extraction, quality and validation

All included articles were obtained and read in full. Two independent reviewers (Xu and Sun) extracted the data according to predetermined criteria. The Cochrane risk of bias tool was used to assess methodological quality of the trials [24]. The following characteristics were assessed: (i) selection bias (random sequence generation and allocation concealment), (ii) performance bias (patients and participant blinding), (iii) detection bias (assessor blinding), (iv) attrition bias (incomplete outcome data), and (v) reporting bias (selective outcome reporting). As it is virtually impossible to blind the moxibustion therapists from the treatment, we evaluated patients and participant blinding and assessor blinding separately. Our review used 'Low, Unclear and High' as keys for the judgments. The answer Low indicated a low risk of bias, Unclear indicated that the risk of bias was uncertain and the answer High indicated a high risk of bias. Disagreements were resolved by discussion between the two reviewers. If consensus could not be reached, the third reviewer (Du) was consulted for a final decision.

Quantitative data synthesis

In our review, meta-analysis was performed using software RevMan 5.2 (available from the website for free: http://www.ccims.net/revman/download). We calculated risk ratio (RR) and 95% confidence intervals (CIs) on dichotomous outcomes, while the effect of moxibustion on continuous outcomes, mean difference (MD) would be applied in this meta-analysis. In each meta-analysis, the chi-square and I^2 tests were used to measure statistical heterogeneity [24]. Given $I^2 < 50\%$ and $p > 0.1$, a fixed effect model would be applied. The random effect model would be used if articles were considered clinically similar enough [25]. If a sufficient number of studies (at least 10) were available, publication bias would use a funnel plot [26].

Results

Trial flow and study characteristics

The literature search of databases generated 300 citations. We excluded 263 articles on the basis of duplication, title and abstract, leaving 37 full texts. Of these 37 articles, 29 were excluded according to the inclusion criteria, leaving 8 eligible RCTs involving 494 participants for the systematic review. Fig. 1 shows a flowchart of the trial selection process. Seven RCTs [27–34] adopted a two-arm and one [34] adopted a three-arm parallel group design. All of the RCTs originated in China. Three trials tested moxibustion alone [32–34]; moxibustion combined with western medicine was used in five studies [27–31]. Except for one trial [32], the duration of the interventions was mostly 3 months. Key data regarding the 8 included RCTs [27–34] are summarized in Table 1. Acupuncture point selection was based on traditional Chinese medicine (TCM) theory for all of the included RCTs. Five RCTs [27–31] met the ACR efficacy evaluation criteria, whereas the remaining trials [32–34] only

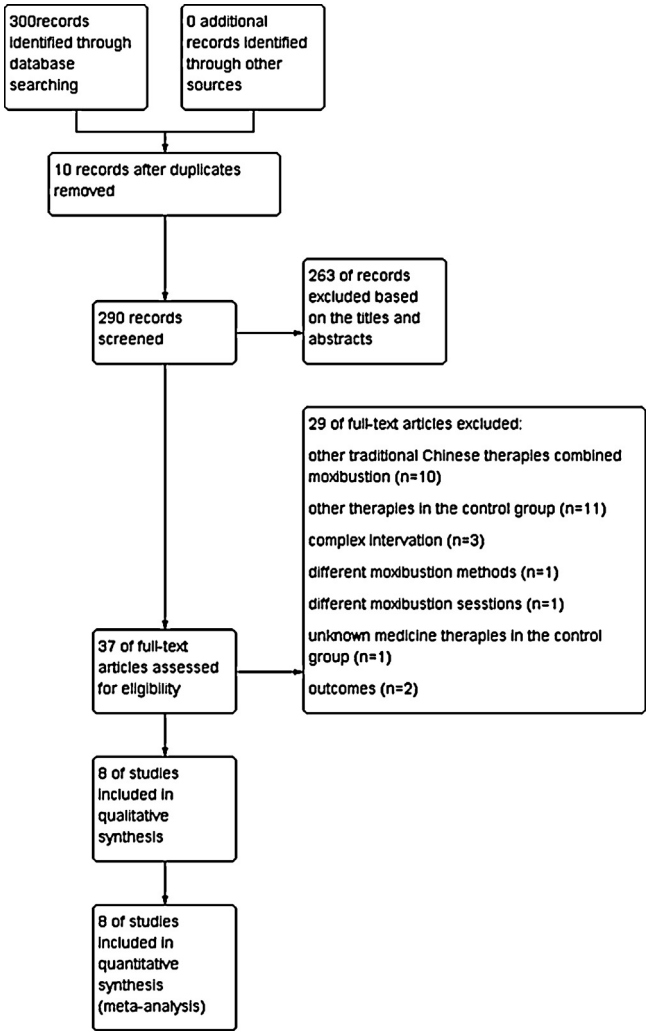

Fig. 1. Flowchart of the trial selection process.

described Chinese medicine efficacy evaluation criteria. The details of the treatment regimens are summarized in Table 2.

Risk of bias

The Cochrane risk of bias was presented in Figs. 2 and 3. Most trials had a relatively small sample size and a high risk of bias. Four of the included trials [27–30] reported appropriate sequence generation methods for the randomization, while one RCT [31] used inappropriate methods and the remaining trials [32–34] did not describe the methods of sequence generation. One RCT [28] conducted concealment of allocation by sealed envelopes, while the remaining trials did not report this information. The authors reported that none of the trials employed patient blinding, and assessor blinding was unclear in all RCTs. Of the 8 included RCTs, four RCTs [27,31,33,34] stated the risk of bias for participant dropout or withdrawal.

Quantitative data synthesis

Western medicine vs Western medicine Plus moxibustion

Table 1
Summary of the randomized controls trials of moxibustion for rheumatoid arthritis.

Subgroup	Study (author/year)	Sample size	Follow-up	Intervention group (regimen)	Control group (regimen)	Main outcomes	Intergroup differences
Western medicine vs Western medicine	Sun (2011) [27]	40	3 months	(A) Indirect moxa (1 session = 30 min, once daily, 5 times/week, 1 month, total 3 sessions, $n = 20$), plus (B). I	(B)Drug therapy (MTX, 10 mg, 1/week), plus NSAIDs, (Celecoxib, 200 mg, 1/day) NSAIDs were used according to patients' conditions, $n = 20$	ACR20 rate	RR, 0.69 [0.36, 1.31], NS
						ACR50 rate	RR, 4.26 [1.06, 17.12], $p = 0.04$
						DAS28	MD, −0.20[−0.50, 0.10]
Plus moxibustion	Chen (2013) [28]	40	3 months	(A) Indirect moxa (1 session = 30 min, once daily, 5 times/week, 3 months, $n = 20$), plus (B).	(B) Drug therapy (MTX, 10 mg, 1/week), plus NSAIDs, (Loxoprofen sodium tablet, 60 mg, 1/day) NSAIDs were used according to patients' conditions, $n = 20$	Response rate	RR, 1.27 [0.96, 1.66], NS
						ACR50 rate	RR, 1.36 [0.85, 2.18], NS
						DAS28 rate	MD, −0.77[−1.09, −0.45]
						withdrawal rate (NSAIDs)	RR, 2.00 [1.12, 3.57], $p = 0.02$
	Huang (2013) [29]	40	3 months	(A) Indirect moxa (1 session = 30 min, once daily, 5 times/week, 3 months, $n = 20$), plus (B).	(B)Drug therapy (Leflunomide tablets, 20 mg, 1/day, plus NSAIDs, NSAIDs were used according to patients' conditions, $n = 20$	Response rate	RR, 1.12 [0.90, 1.38], NS
						ACR20 rate	RR, 1.15 [0.77, 1.74], NS
						ACR50 rate	RR, 1.60 [0.63, 4.05], NS
						ACR70 rate	RR, 4.0 [0.49, 32.72], NS
						DAS28	MD, −0.29[−1.15, 0.57]
Western medicine vs Western medicine	Li (2006) [30]	60	3 months	(A) Indirect moxa (1 session = 30 min, 5 days/week, 3 months, $n = 30$), plus (B)	(B) Drug therapy (MTX, 10 mg, 1/week plus NSAIDs, (loxoprofen, 60 mg, 3/day or meloxicam 15 mg, 1/day) NSAIDs were used according to patients' conditions, $n = 30$	Response rate	RR, 1.39 [1.00, 1.94], NS
						ACR50 rate	RR, 1.57 [1.01, 2.44], $p = 0.04$
						with drawal rate (NSAIDs)	RR, 1.73 [1.18, 2.55], $p = 0.01$
Plus moxibustion	Liu (2006) [31]	62	3 months	(A) Indirect moxa (1 session = 30 min, once daily, 5 times/week, 3months, $n = 31$), plus (B)	(B) Drug therapy (MTX, 10 mg, 1/week plus NSAIDs, (Loxoprofen sodium tablets, 60 mg, 3/day) NSAIDs were used according to patients' conditions, $n = 31$	Response rate	RR, 1.33 [1.04, 1.72], $p = 0.03$
						ACR50 rate	RR, 1.39 [1.00, 1.94], NS
						withdrawal rate (NSAIDs)	RR, 1.82 [1.07, 3.10], $p = 0.03$
Western medicine vs moxibustion	Gong (2007) [32]	65	*n*.r.	(A) Indirect moxa (1 session = *n*.r., once every 2 days, 30 days, total 6 sessions, $n = 33$)	(B) Drug therapy (meloxicam tablets, 75 mg, 1/day, $n = 32$)	Response rate	RR, 1.34 [1.01, 1.77], $p = 0.04$
Western medicine vs moxibustion	Wang (1999) [33]	93	3 months	(A) Indirect moxa (1 session = *n*.r., once daily or once every 2 days, 50 times/session, total 1 session., $n = 64$)	(B) Drug therapy (Penicillamine, 0. 375–0. 75 g/day, $n = 29$)	Response rate	RR, 1.13 [0.92, 1.40], NS
	Yang (2007) [34]	94	3 months	(A) Indirect moxa (1 session = n.r., once daily, 50 times/session, total 1 session, $n = 31$) (B) Smokeless moxa (1 session = n.r., once daily, 50 times/session, total 1 session, $n = 33$)	(C) Drug therapy (Penicillamine, $n = 30$)	Response rate	B vs. C: RR, 1.12 [0.83, 1.51], NS A vs. C: RR, 1.14 [0.85, 1.52], NS

ACR, American College of Rheumatology; DAS28, disease activity score; MD, mean difference; Moxa, moxibustion; MTX, methotrexate; n.r., not reported; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio.

Table 2
Summary of the treatment points and other information related to the treatments.

Study (author/year)	Types of moxibustion	Treatment points	Acupoints' rational theory	Adverse events
Sun (2011) [27]	Aconite cake-separated moxa	RN 4, ST36	TCM theory: Invigorate the kidney and nourish the stomach and spleen	n.r.
Chen (2013) [28]	Aconite cake-separated moxa	RN 4, ST36	TCM theory: Invigorate the kidney and nourish the stomach and spleen	None related to moxa.
Huang (2013) [29]	Aconite cake-separated moxa	RN 4, ST36	TCM theory: Invigorate the kidney and nourish the stomach and spleen	n.r.
Li (2006) [30]	Aconite cake-separated moxa	RN 4, ST36	TCM theory: Invigorate the kidney and nourish the stomach and spleen	None related to moxa
Liu (2006) [31]	Aconite cake-separated moxa	RN 4, ST36	TCM theory: Invigorate the kidney and nourish the stomach and spleen	None related to moxa
Gong (2007) [32]	Herbal cake-separated moxa	DU 13, BL 11, BL 17, BL 20, BL 23	TCM theory: Warm the kidney and spleen, expel wind and dampness, and strengthen tendons and bones.	n.r.
Wang (1999) [33]	Aconite cake-separated moxa	Group 1: RN 17, RN 12, RN 6, RN8, ST 36 Group 2: BL17, BL 18, BL 20, DU 4 Two group points were used interchangeably in every treatment.	TCM theory: not report in details TCM theory: not report in details	None related to moxa.
Yang (2007) [34]	Ginger cake-separated moxa	Group 1: RN 17, RN 12, RN 6, RN8, ST 36 Group 2: BL17, BL 18, BL 20, DU 4 Two group points were used interchangeably in every treatment.		n.r.

ACR, American College of Rheumatology; TCM, traditional Chinese medicine; n.r., not reported.

ACR20 rate. There were two RCTs [27,29] ($n = 80$), which used ACR20 rate as a measure of the effects for improving RA. The two studies both showed no statistically significance between the groups on the ACR20 rate. The meta-analysis suggested that, compared with Western medicine therapy, moxibustion plus Western medicine therapy had no statistically significant favorable effects on the ACR20 rate [RR = 0.94, 95% CI (0.66,1.33), $p = 0.72$] (Fig. 4)

ACR50 rate. There were five RCTs [27–31] ($n = 242$), which used ACR50 rate as a measure of the effects for improving RA. Two of the studies [27,30] showed statistically significant positive effects on the ACR50 rate between groups, while the other three [28,29,31] did not. The result of meta-analysis suggested that, compared with Western medicine therapy, moxibustion plus Western medicine therapy had statistically significant favorable effects in improving the ACR50 rate [RR = 1.57, 95% CI (1.25, 1.99), $p = 0.0001$] with low heterogeneity [$Chi^2 = 2.87$, $p = 0.58$, $I^2 = 0\%$] (Fig. 4).

Response rate. There were four RCTs [28–31] ($n = 202$), which used response rate as an outcome on the effects for improving RA. Only one [31] research indicated significant positive effect on response rate between groups, but the pooled meta-analysis showed significantly superior effects of moxibustion plus Western medicine therapy when compared with Western medicine therapy. [RR = 1.28, 95%CI (1.12, 1.47), $p = 0.0004$] with low heterogeneity [$Chi^2 = 1.96$, $p = 0.58$, $I^2 = 0\%$] (Fig. 4).

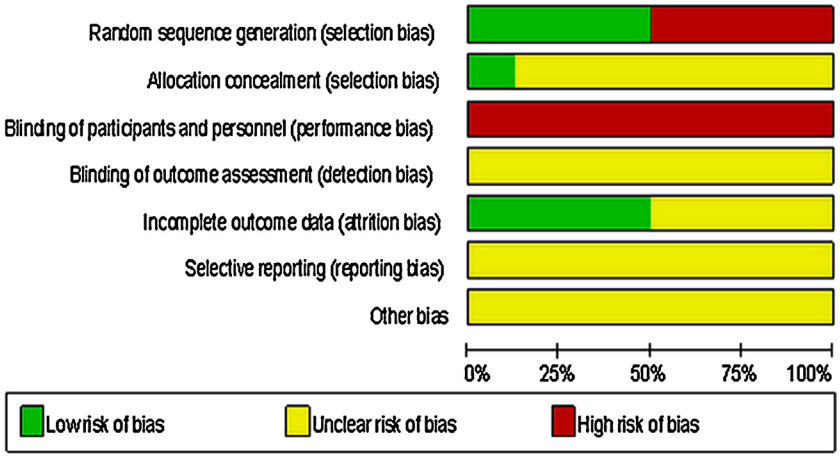

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

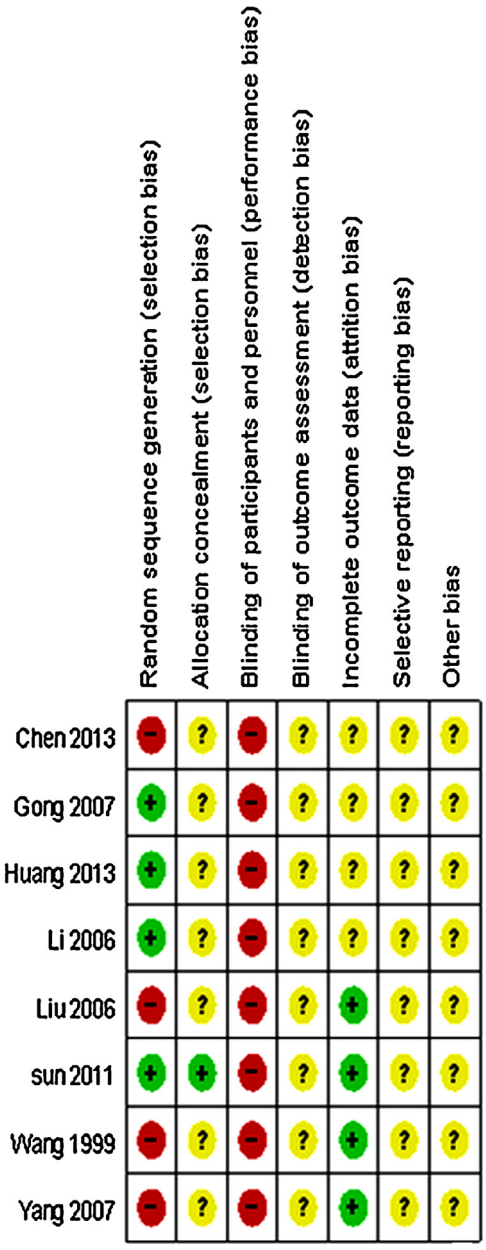

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

DAS28. There were three RCTs [27–29] ($n = 120$), which used DAS28 to measure the disease activity score of the RA. The result of meta-analysis showed that, compared with Western medicine therapy, moxibustion plus Western medicine therapy had favorable but not statistically significant effects in improving RA conditions. [MD = −0.45, 95%CI (−0.89, −0.01), $p = 0.05$] (Fig. 5).

Of the remaining studies, one study [29] ($n = 40$), which was not included in the meta-analysis, used ACR70 rate as a measurement. The moxibustion plus Western medicine therapy on ACR70 rate indicated no statistically significant effect when compared with Western medicine therapy. [RR = 4.0, 95%CI (0.49, 32.72), $p > 0.05$].

Western medicine vs moxibustion

Response rate

Three RCTs ($n = 252$) tested the effects of moxibustion compared with western medicine therapies in patients with RA. Only one RCT [32] suggested that, compared with Western medicine therapies alone, moxibustion therapy showed favorable statistically significant results on response rate. The meta-analysis of the three eligible trials showed significantly positive effects of moxibustion on response rate. [RR = 1.18, 95%CI (1.03, 1.35), $p = 0.02$] with high heterogeneity [$\text{Chi}^2 = 1.11$, $p = 0.77$, $I^2 = 0\%$] (Fig. 6)

Adverse effects

Of included eight trials, four [28,30,31,33] RCTs assessed adverse effects while the other four [27,29,32,34] RCTs did not. Several common adverse outcomes (nausea and vomiting, the risks of liver injury, leucopenia, rash, etc.) from drug therapy in moxibustion combined with western medical therapies were reported in these trials [27,29,32,34].

Discussion

Our studies suggested that moxibustion may have beneficial effects for treating RA. However, considering the high risks of bias of all included trials, and the relative small sample size in each group, these positive results should be interpreted with caution.

A meta-analysis published in 2011 summarized and critically evaluated the effectiveness of moxibustion for major rheumatic conditions (including 4 studies on RA) [17]. They found a superior but limited evidence of impact and effectiveness related to rheumatic conditions. Nevertheless, a subgroup analysis of RA showed no statistically significant differences in the response rate of moxibustion versus conventional drug therapy. Moreover, when compared with the drug therapy, the subgroup analysis also failed to show the favorable effects of moxibustion plus drug therapy on the response rate. These results from previous reviews [17] seemed to be inconsistent with our systematic review. Currently, in our review, more new RCTs published after 2010 were also identified and successfully updated the available evidence concerning moxibustion therapy. Therefore, it is important to consider that a meta-analysis should be updated periodically as new RCTs are published. However, considering a lot of low methodological quality RCTs in our meta-analysis, we still cannot reverse the results from the previous study in terms of the available evidence.

We assessed the methodological quality of primary studies using the risk of bias assessment tool from the Cochrane Handbook. In this context, most of the included studies in this review showed the high risk bias in various aspects. First of all, trials with inadequate random sequence generation and inadequate allocation concealment may be subject to selection bias and are more likely to overestimate the results of the outcome measures [35,36]. For adequate random sequence generation, high risk of bias was given to 50% of the included studies. Though some studies claimed to use randomized trials, they failed to

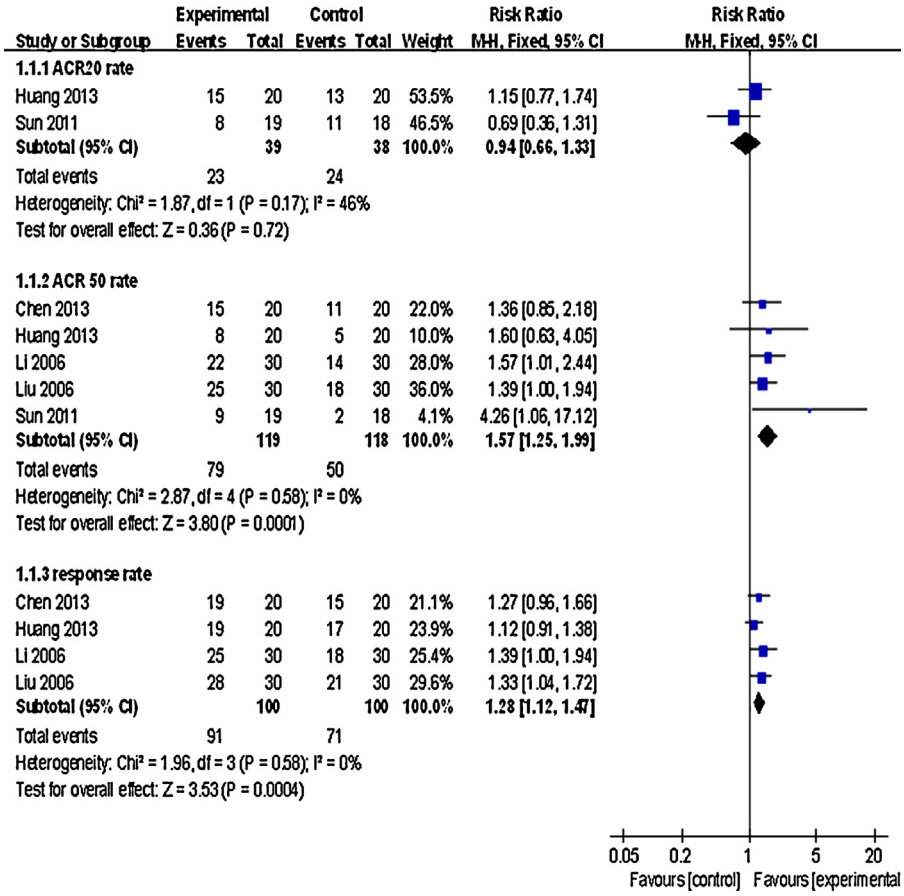

Fig. 4. Western medicine Plus moxibustion therapy vs Western medicine therapy on ACR20 rate, ACR50 rate and response rate.

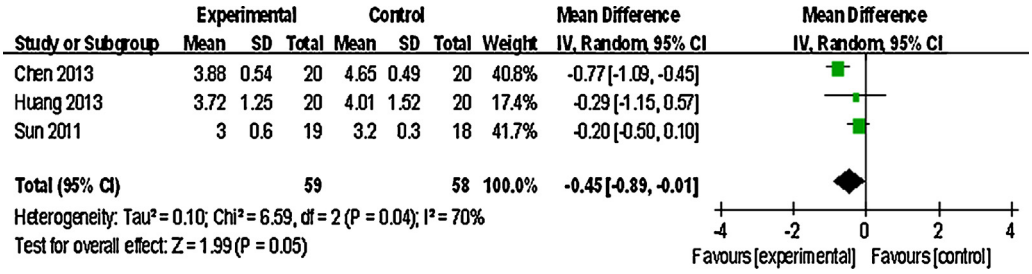

Fig. 5. Western medicine Plus moxibustion therapy vs Western medicine therapy on DAS28.

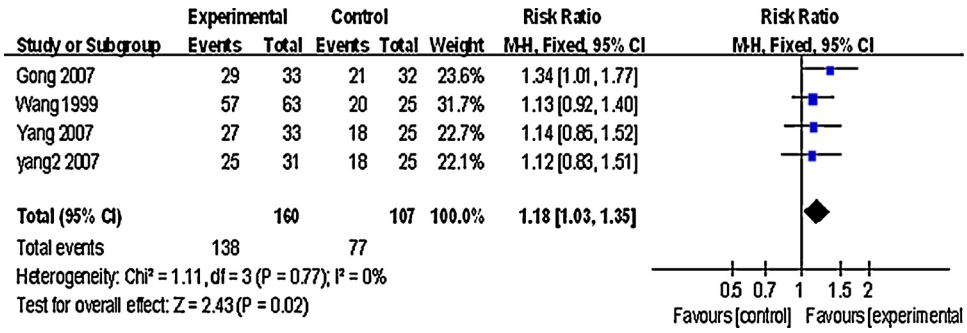

Fig. 6. Moxibustion therapy alone vs Western medicine therapy on response rate.

describe in detail the process of randomization. Additionally, one RCT [28] reported that participants were assigned to the control and intervention groups based on the dates they were admitted to the hospitals, which should not be considered as adequate randomization. For the allocation concealment, the group assignment was adequately concealed in only 12.5% of included studies and the rest of the studies were given unclear risk of bias, mostly due to a lack of related reporting. Therefore, results of this meta-analysis may seem to be more optimistic than it should be. Furthermore, details of drop-outs and withdrawals were described in only 50% of included trials. This may lead to exclusion or attrition bias [37]. Last but not least, due to the nature of moxibustion interventions, participant blinding was not always feasible. However, no single included study mentioned blinding assessors. Hence, selection, performance, attrition and detection biases were prevalent in most of the included studies.

Having a placebo or sham moxibustion comparable to the specific effects of moxibustion may be essential and critical in the randomized controlled trial. In all included studies, none tested the different effects between the sham moxibustion and the specific effects of moxibustion. Hence, one problem with clinical trials of moxibustion is finding a suitable placebo control. Considering that the possible effects of moxibustion could come from stimulating acupuncture points with heat, sham moxibustion might include treating outside acupuncture points on non-acupuncture points or preventing heat stimulation on acupuncture points or areas. Currently, two placebo or sham moxibustion methods have been proposed for trials of moxibustion, and these could achieve patient and practitioner blinding [38,39]. However, in terms of their reliability, some discrepancies may continue to exist. The main drawback of these sham moxibustion methods is the lack of the essential characteristics of the moxibustion, the smoke, smell and the sensation [40]. Recently, a pilot placebo-controlled trial has assessed the effect of moxibustion treatment with a sham control [41]. Nevertheless, the number of patients was too small to generate reliable findings. Therefore, there are no universally accepted placebo or sham moxibustion devices, and the adequate sham moxibustion devices may be created in the future.

One argument for using moxibustion for treating RA might be that it is safer than western medicine [42]. In this study, Four RCTs [27,29,32,34] reported that adverse events (nausea and vomiting, the risks of liver injury, leucopenia, rash, etc.) were from drug therapy in moxibustion combined with western medical therapies group. Moxibustion may be a safe treatment for RA in this study. However, the probable adverse events of moxibustion including allergic reactions, burns and infections have been reported in previous research [43,44]. Therefore, future trials should provide more details about any adverse events associated with moxibustion or safety assessment.

Another important issue that should be discussed is the culture-specific efficacy evaluation of RA. Subjects in five RCTs met the ACR criteria [27–31], whereas the remaining studies [32–34] only described Chinese medicine assessment. In contrast with Korea and Japan, there are many disparities in the widely published and accepted standardized evaluations of efficacy in the field of Complementary and Alternative Medicine [45]. Hence, in addition to Chinese medicine assessment, for future studies, it is recommended that trials should use ACR outcome measures to evaluate the effectiveness of moxibustion for treating RA.

Assuming that moxibustion is a beneficial treatment for RA, possible mechanisms of action are of interest. In modern research, the widely accepted view of the mechanisms operating is that of anti-inflammation and immunoregulation theory [46]. Moxibustion can reduce the release of inflammatory mediators [interleukin (IL)-1, interleukin (IL)-6, tumor necrosis factor (TNF), etc.], regulate the central neurotransmitter level [nitric oxide (No)], improve the body's immune function, and protect the thymus, spleen and other immune organs [46–48]. Another hypothesis is the thermal stimulation effect theory. Heat stimulated by burning moxa transferred to skin, which is recognized by the thermal sensory receptors as invasive stimulation. When this stimulation activates on the thermal sensory receptors, the signal enters the central nervous system through nerve fibers, and the therapeutic effects can be produced [49]. In a recent arthritic rat model study, moxibustion seemed to have positive effects on the rat's muscle regeneration by inhibiting the TGF-B1 and myostatin and activating IGF-1 [50]. None of these theories are, however, currently fully established. Hence, there is still a great distance to go before we fully understand the mechanism involved with moxibustion.

Study limitations

This review may have several important limitations. First of all, this systematic review had a high risk of bias, which seemed to result in the positive results we found. In the future, in order to avoid bias, we suggest that authors refer to the recent extension of the Consolidated Standards of Reporting Trials (CONSORT) statement for trials of moxibustion interventions [51,52]. In addition, the sample size of included studies was very small. Currently, there are no rules regarding sample-size requirements for a meta-analysis. However, in order to avoid false positive conclusions due to an insufficient number of patients, the total number of patients included in a meta-analysis should be at least as large as that in a well-designed and optimally powered RCT [53]. Therefore, a larger total number of patients may be needed in the future studies. Furthermore, a potential source of bias of this review may originate from the search strategy. The search strategy utilized is more likely to detect English and Chinese language publications. Considering that moxibustion therapy is also one of the most widely used basic oriental medical techniques in Korea and Japan, it is possible that relevant publications have not been identified. Hence, more databases should be searched to identify publications in Korean and Japanese languages other than English and Chinese. Additionally, due to the number of pooled studies was too small, it was not suitable for us to formally test asymmetry in the funnel plot. Moreover, the publication bias in favor of positive conclusions about moxibustion therapies may generate this meta-analysis [54]. Lastly, all include RCTs were conducted on Chinese populations; therefore the results are only limited to Asian populations. Further studies should include

non-Asian subjects to test the effectiveness of moxibustion on different populations.

In the future, there is a need for robust, methodologically sound, randomized controlled trials of adequate statistical power and validated outcome measurements to evaluate the efficacy as well as safety of moxibustion for RA. Furthermore, if possible, the long-term effects of moxibustion and assessor blinding should be taken into the consideration in the future trials.

Conclusions

It is difficult to draw firm conclusions that moxibustion is an effective intervention for treating RA due to the small sample size of eligible RCTs and the high risk of bias among the available RCTs. Further rigorous RCTs are warranted but need to overcome methodological shortcomings of the existing evidence.

Conflict of interests

No conflict of interests declared.

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Appendix A. Search strategies

MEDLINE

1. arthritis, rheumatoid [mh]
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) adj3 (arthrit* or artrit* or diseas* or condition* or nodule*)) [tw]
3. 1 or 2
4. Moxibustion [mh]
5. moxa [tw]
6. 4 or 5
7. 3 and 6
8. randomized controlled trial [pt]
9. controlled clinical trial [pt]
10. randomized [tiab]
11. placebo [tiab]
12. clinical trials as topic [mesh: noexp]
13. randomly [tiab]
14. trial [ti]
15. or/8-14
16. animals [mh] NOT humans [mh]
17. 15 not 16
18. 7 and 17

Embase

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) adj3 (arthrit* or artrit* or diseas* or condition* or nodule*)).af.
3. 1 or 2
4. exp Moxibustion/
5. moxa .af.
6. 4 or 5
7. 3 and 6
8. (random* OR factorial* OR crossover* OR placebo*).af.
9. exp crossover-procedure/or exp double-blind procedure/or exp randomised controlled trial/or single-blind procedure/
10. 8 or 9
11. 7 and 10

Cochrane Central Register of Controlled Trials

#1 MeSH descriptor Arthritis, Rheumatoid explode all trees
#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab
#3 (#1 OR #2)
#4 MeSH descriptor Moxibustion explode all trees
#5 moxa*:ti,ab
#6 (#4 OR #5)
#7 (#3 AND #6)

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